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LETTER TO THE EDITOR

A standardized nomenclature for adenosine deaminases that act on RNA

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In 1987, two laboratories involved in antisense RNA experiments made intriguing observations about the fate of double-stranded RNA (dsRNA) injected into early *Xenopus laevis* embryos (Rebagliati & Melton, 1987; Bass & Weintraub, 1987). For example, it was noticed that dsRNA, after incubation in an embryo, had an altered mobility on a native gel (Bass & Weintraub, 1987), and was more sensitive to digestion by single-strand specific ribonucleases (Rebagliati & Melton, 1987). Based on their observations, these laboratories postulated that the dsRNA had been acted on by an *unwinding activity*. Soon after, similar observations were made in mammalian cells (Wagner & Nishikura, 1988), and in this case, the activity was called an *unwindase*.

Subsequent work led to the discovery that the unwinding activity catalyzed the covalent modification of adenosine, to produce inosine (Bass & Weintraub, 1988; Wagner et al., 1989). It became clear that the activity did not actually separate the two strands of a dsRNA molecule. Rather, the RNA became more single-stranded in character because stable AU base pairs were changed to the considerably less stable IU base pair. To describe more accurately its catalytic activity, the activity was renamed the *unwinding/modifying activity*.

In further studies, the mechanism of the activity was shown to involve an adenosine deamination (Polson et al., 1991), and the enzyme was purified from frogs (Hough & Bass, 1994) and mammalian tissues (Kim et al., 1994a; O'Connell & Keller, 1994). Depending on the laboratory working on the enzyme, it was then called dsRAD (dsRNA adenosine deaminase) or DRADA (dsRNA adenosine deaminase). Nomenclature issues became more complicated when a second, distinct, dsRNA adenosine deaminase was discovered based on its ability to differentially modify certain sites in glutamate receptor B (gluR-B) pre-mRNAs (Melcher et al., 1996b). This enzyme was called RED1 (dsRNA specific editase 1). In addition, when confronted with cataloging of the human dsRAD gene (Weier et al., 1995), the human genome organization (HUGO) nomenclature committee proposed the enzyme be called ADAR.

To facilitate future discussions of all of these enzymes, and to make the literature more accessible to those in other scientific disciplines, we propose that a new nomenclature be adopted in which all enzymes that deaminate adenosines within RNA be named in a standardized manner, based on the recommendations of the HUGO committee.

In keeping with the three-letter acronym used for adenosine deaminases that act on nucleosides (ADA), enzymes that catalyze the same reaction on RNA will be called ADARs, for adenosine deaminases that act on RNA. The enzymes can be referred to generically as ADARs. Based on in vitro activity assays, two distinct types of ADARs have been characterized, and these will be called ADAR1 and ADAR2 (see Table 1). In

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TABLE 1. New names for adenosine deaminases that act on RNA.

Old names	New name	Observed in	Alternate splice forms	M.W. (kDa)[a]	Deaminase activity
dsRAD	ADAR1	X. laevis[b]	xADAR1.1a, b[c]	139[c]	Yes
DRADA			xADAR1.2a, c[c]		Yes
ADAR		Rat[d]	n.d.[k]	130	Yes
ADAR-a		Human[e]	hADAR1a, b, c	136, 133, 131	Yes
		Chicken[f]	n.d.[k]	140	Yes
RED1[g]	ADAR2	Rat[h]	rADAR2a, b, c, d[g]	78, 77, 76, 74	Yes
ADARB1		Human[i]	hADAR2a, b, c, d[g]	77, 81, 78, 74	Yes
DRADA-2					
RED2	None (ADAR-like)	Rat[j]	n.d.[k]	82	?
ADARB2					
TENR	None (ADAR-like)	Mouse[l]	n.d.[k]	68	?
T20H4.4	None (ADAR-like)	*C. elegans*[m]	n.d.[k]	55	?

[a]All molecular weights were predicted from cDNAs, except that for the chicken enzyme, which was determined by SDS-PAGE of the endogenous protein.

[b]Hough and Bass (1997).

[c]There appear to be two expressed genes in *Xenopus*, xADAR1.1 and xADAR1.2, previously called dsRAD1 and dsRAD2, respectively. Only the molecular weight of the protein encoded by xADAR 1.1a has been determined.

[d]O'Connell et al. (1995).

[e]Kim et al. (1994b); Patterson and Samuel (1995); O'Connell et al. (1995); Liu et al. (1997).

[f]Herbert et al. (1995).

[g]RED1 corresponds to splice form ADAR2a, which has been referred to previously as hRED1-S or DRADA2a.

[h]Melcher et al. (1996b); S. Rueter and R. Emeson, in prep.

[i]Lai et al. (1997); O'Connell et al. (1997); Mittaz et al. (1997); Gerber et al. (1997).

[j]Melcher et al. (1996a).

[k]n.d., not detected or not determined.

[l]Schumacher et al. (1995).

[m]U00037; R. Hough, A. Lingam, and B. Bass, in prep.

vitro studies show that both ADAR1 and ADAR2 can promiscuously modify completely base paired dsRNA of artificial sequence, but they have different specificities for editing sites within their putative endogenous substrates (Melcher et al., 1996b; Lai et al., 1997), in which base paired regions are sometimes interrupted by mismatches, bulges, and loops. For example, incubation of ADAR1 with gluR-B RNA shows efficient deamination of adenosines at the +60 intronic site and the R/G site, but very little deamination of the adenosine at the Q/R site. In contrast, ADAR2 is very efficient at deaminating both the Q/R and R/G site adenosines, but inefficient at modifying the +60 intronic adenosine. (See Melcher et al., 1996b and Lai et al., 1997 for a description of the various modification sites in gluR-B RNA.)

As indicated in Table 1, alternative splice forms of ADAR1 and ADAR2 will be specified by a letter of the alphabet, in lower case, following the enzyme name. Whenever possible, the protein derived from the longest RNA will be given the letter a, that from the next longest, b, etc. When necessary for increased clarity, the organism from which the enzyme is derived will be indicated by a small letter preceding the word ADAR (e.g., rat, rADAR; *Xenopus*, xADAR; *Caenorhabditis elegans*, ceADAR).

A number of cDNAs have been identified that are clearly related to ADAR1 and ADAR2, but have not yet been proven to have deaminase activity. We propose that these enzymes be discussed as ADAR-like, and retain their given name until it is clear whether they represent a new type of ADAR (e.g., ADAR3), or can be placed into an existing group. Advice in regard to naming future enzymes should be directed to one of the authors of this manuscript, who will then consult with all co-authors.

Finally, we note that our proposed nomenclature system makes no assumptions in regard to homologues between organisms.

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